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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/873,546	06/04/2001	Geoff J. Clark	NIH-05080	7592

45733 7590 01/14/2005

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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/873,546	CLARK ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,30,31 and 35-66* is/are pending in the application.

4a) Of the above claim(s) *53-63* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,30,31,35-52 and 64-66* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 10/22/04.

Claims 6-16, 29, and 32-34 were cancelled and claims 40-66 were added as requested.

Claims 1-4, 30, 31, 35-66 are pending.

Claims 1-4, 30, 31, 35, 36 (in part), 37-43, 44-48 (in part), 49-52, and 64-66 are under consideration in this Office Action. Claims 36 and 44-48 are drawn in part to non-elected inventions, and claims 53-63 are fully drawn to non-elected inventions, as discussed more fully below.

Election/Restrictions

Newly submitted claims 53-63 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 53-63 are directed to methods of diagnosing , or detecting a predisposition to, cancer in a mammal. The other pending claims are drawn to nucleic acids. These inventions are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the nucleic acids can be used to produce the encoded protein for the production of antibodies against the protein. This represents a materially different process of using the product, so the inventions are properly restricted. Since

applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 53-63 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim 36 has been amended to embrace inventions that are independent and distinct. Similarly, newly submitted claims 44-48 embrace inventions that are independent and distinct. These claims embrace a host cell or a non-human organism comprising a nucleic acid molecule encoding SEQ ID NO:5 or its complement. The scope of the claims directed to host cells was examined previously. However, in view of the specification at page 29, lines 11-17, the scope of the claims directed to non-human organisms comprising the nucleic acid embraces transgenic animals. This invention was not previously examined and is patentably distinct from the scope directed to host cells for the following reasons. Host cells comprising nucleic acids encoding SEQ ID NO:5 are classifiable in class 435 subclasses 252.3 or 325, whereas transgenic animals are classified in class 800, subclass 8. Search and examination of claims directed to host cells comprising nucleic acids encoding SEQ ID NO:5 would not require consideration of the enablement of making and using transgenic animals comprising nucleic acids encoding SEQ ID NO:5. As such the search and examination of transgenic animals comprising nucleic acids encoding SEQ ID NO:5 represents an undue burden on the Examiner, and restriction is warranted. As such claims 36 and 44-48 will be examined only to the extent that they embrace the originally elected subject

matter, i.e. host cells comprising the claimed nucleic acids. See 37 CFR 1.142(b) and MPEP § 821.03.

Rejections Withdrawn

The previous rejections of claims 35-39 under 35 USC 112, second paragraph are withdrawn in view of Applicant's amendments necessitating new grounds of rejection.

The rejections of claims 1-4 and 35-39 under 35 USC 112, first paragraph for new matter is withdrawn in view of Applicant's amendments. Note that claim 4 as amended is newly rejected for new matter.

The rejections of claims 35-39 under 35 USC 112, first paragraph for lack of adequate written description and enablement is withdrawn in view of Applicant's amendments rendering these claims indefinite.

Claim Objections

Claims 36 and 44-48 are objected to because they recite non-elected subject matter, as discussed above, i.e. non-human organisms comprising particular nucleic acids. These claims are also objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims 36 and 44-48 depend from claims directed to isolated or purified nucleic acid molecules, but claims 36 and 4-48 do not contain isolated or purified nucleic acid molecules, instead, the nucleic acid molecules must be contained within a host cell or

non-human organism. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35-39 and 44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 35-39 and 44 are indefinite because they require a nucleic acid that has at least 30% identity with SEQ ID NO:5. SEQ ID NO:5 is an amino acid sequence, and so cannot have identity with any nucleic acid sequence. As a result the claims do not make sense. The Examiner considers it likely that Applicant intended to require that the claimed nucleic acid must encode a polypeptide with 30% identity to SEQ ID NO:5. Note that the comments on the enablement, written description, and novelty of such claims are set forth below following rejections under 35 USC 112, first paragraph and 35 USC 102.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claim 65 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 65 requires a pharmaceutical composition manufactured "according to the Current Good Manufacturing Practice for Finished Pharmaceuticals (21 CFR 211)." There is no written support for this limitation in the specification, and it represents new matter.

Enablement

Claims 41, 43, 46, 48, 50, and 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated or purified nucleic acids encoding SEQ ID NO:5 or fragments thereof that inhibit tumor cell growth, does not reasonably provide enablement for nucleic acids encoding polypeptides that inhibit tumor cell growth and are identical to SEQ ID NO:5, or fragments thereof, except for one or more conservative amino acid substitutions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 41, 43, 46, and 48 are drawn to the genus of nucleic acids encoding "a Rig protein (SEQ ID NO:5) having one or more conservative amino acid substitutions, or

a portion thereof, wherein the protein or portion thereof inhibits growth of a tumor cell when contacted with said tumor cell." The specification provides no limiting definition of what is and is not a Rig protein, and defines conservative substitution as substitution with "a different amino acid having similar chemical properties." See e.g. page 21, lines 3-7. As such, the genus of encoded polypeptides must be less than or equal to SEQ ID NO:5 in length, but need have no sequence identity whatsoever with SEQ ID NO:5, as long as it contains at least one amino acid that has a similar chemical properties.

The specification provides guidance as to the function of SEQ ID NO:5, which is a member of the Ras protein superfamily, see e.g. Figs. 2 and 3. This protein is expressed in fetal and adult brain and heart, but not in a variety of other tissues. Expression is reduced or zero in some tumor derived neuronal cell lines and tumor-derived tissue samples, but appears normal in others (see e.g. Fig. 12, lanes 3, 4, 6, and 9-12). Constitutive expression of SEQ ID NO:4 inhibits focus formation in NIH 3T3 cells. The protein antagonizes Ras-dependent Elk-1 transcription factor activity, and inhibits the growth of U251 and A673 neuronal tumor-derived cells when expressed ectopically in these lines. An S21N mutation of SEQ ID NO:5 (analogous to Ras S17N) causes transformation when expressed in NIH 3T3 cells. Finally, SEQ ID NO:5 coprecipitates with Raf-1, a kinase which is regulated by H-Ras and K-Ras. However, the specification fails to teach what are the minimum sequence and functional characteristics a given polypeptide must have in order to inhibit tumor cell growth, and exemplifies no conservative substitution mutation that preserves tumor cell growth inhibition activity of SEQ ID NO:5.

At the time the invention was filed the Ras protein superfamily contained about 150 members which functioned to transduce a wide variety of signals in cells. See Paduch et al (Acta Biochemica Polonica 48(4): 829-850, 2001) page 830, column 1, first line of last paragraph. These proteins all comprise a guanine nucleotide binding domain with a high affinity for GTP or GDP, and low (but extremely variable within the superfamily) catalytic activity. The nucleotide binding site also contributes to the binding of effector molecules which are activated by Ras and which mediate the wide variety of cellular responses. The phosphorylation state of the nucleotide in the binding site regulates the activity of the Ras protein, (GDP activates Ras, and GTP inactivates Ras), and influences recognition and binding of effector molecules. So, structural differences between Ras molecules govern the rate at which GTP is hydrolyzed as well as the identity of effector molecules with which they interact, and consequently the nature of signals that are transduced. See page 833, column 1, last full paragraph of Paduch. Although various Ras nucleotide binding sites are well known and highly conserved, it is unclear what governs the substantial kinetic differences in GTP/GDP exchange observed in the various Ras proteins. While the Raf-1 binding site of Rap-1A is known in the art (see Paduch at paragraph bridging pages 837 and 838), the specification does not disclose the Raf-1 binding site of SEQ ID NO:5, or what amino acids can be mutated substituted while preserving this function,, nor the claimed function of inhibiting tumor cell growth.

Generally speaking, the effects of amino acid substitutions on polypeptide activity are unpredictable. While it is known that many amino acid substitutions are generally

possible in any given protein, certain positions in a polypeptide sequence are critical to the protein's structure/function relationship, such as various sites or regions where the biological activity resides or regions directly involved in binding, stability or catalysis, or which provide the correct three-dimensional spatial orientation for biologically active binding sites, or which represent other properties or characteristics or properties of the protein. These or other regions may also be critical determinants of activity. These regions can tolerate only relatively conservative substitutions, or no substitutions. See Bowie et al (1990). The prior art teaches that the effects of amino acid substitutions and deletions on protein function were highly unpredictable. Rudinger (In Peptide Hormones J.A. Parsons, Ed. University Park Press, Baltimore, 1976, page 6) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study." Furthermore Ngo et al (In The Protein Folding Problem and Tertiary Structure Prediction, K. Merz Jr. and S. Legrand, Eds. Birkhauser, Boston, 1994, see page 492) teaches that "[i]t is not known if there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. Decades of research have failed to produce such an algorithm". In the specific case of Ras proteins, Paduch teaches that the effects on the activity of the protein of mutations in the nucleotide binding site are unpredictable. Furthermore, site directed mutagenesis studies have shown that mutations affecting nucleotide binding, and therefore signal transduction, are not limited only to the nucleotide binding site, but are found in segments well outside the nucleotide binding site. See paragraph bridging

columns 1 and 2 on page 834. Because neither the prior art nor the specification provides adequate guidance as to how to generally predict the effects of amino acid substitutions within even the highly conserved nucleotide binding site of Ras proteins, and because the specification fails to teach what are the structural limitations that define Rig polypeptides, one of skill in the art could not determine without undue experimentation what sequences other than SEQ ID NO:5 comprise the claimed activity of SEQ ID NO:5, and could not make such proteins without undue experimentation. One might argue that it would not be undue experimentation to express and assay polypeptides individually using the assays taught in the specification, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. The specification fails to provide any theoretical framework which can be used to accurately predict which amino acid substitutions will adequately maintain SEQ ID NO:5 tumor cell growth inhibition activity. In the absence of such guidance, one of skill in the art would have to perform undue experimentation in order to make the invention commensurate in scope with the claims.

As currently written, instant claims 35-39 and 44 are indefinite for the reasons set forth above. However, it is noted that Applicant may have intended these claims to be

drawn to nucleic acids that encode polypeptides that inhibit tumor cell growth and are at least 30% identical to SEQ D NO:5. In the interest of compact prosecution, Applicant is advised that such claims would lack enablement for the reasons set forth above, i.e. the unpredictable nature of Ras protein structure/function relationships and the effects of mutations on Ras-related protein activity, combined with a lack of guidance in the specification regarding what mutations could be made to SEQ ID NO:5 while still preserving the claimed activity of tumor cell growth inhibition.

Furthermore, the specification would not provide an adequate written description for such claims for the following reasons. The written description requirement can be satisfied for genus claims by disclosure of a representative number of species of the claimed genus. Disclosure may be by reduction to practice, drawings, or complete structural description, or by disclosure of relevant identifying characteristics such as a known or disclosed correlation between structure and function that is common to the members of the genus. The specification discloses Noey2, a tumor suppressor protein that is 46% identical to SEQ ID NO:5 that is a species of the clamed genus. The specification also discloses an S21N mutation of SEQ ID NO:5 (analogous to Ras S17N) that causes transformation when expressed in NIH 3T3 cells, and so is not a member of the claimed genus. No other nucleic acid is disclosed that encodes a protein that is at least 30% identical to SEQ ID NO:5 and inhibits tumor cell growth.

The genus of proteins that are greater than 30% identical to SEQ ID NO:5 includes several that are not known to inhibit tumor cell growth. See for example, rap2 (Medline document number 8204955), which is 50%, and National Center for

Biotechnology Information printouts for Accession Nos. NP_649948, and NP_660252, which disclose proteins that are 93%, and 75% identical, respectively. Alignments are attached.

While claims to nucleic acids that combine a structural limitation with a functional limitation may sometimes be considered to have an adequate written description, in this case the stuctural and functional limitations define a genus that is so broad that the disclosed structural characteristic does not correlate with the functional characteristic. For example, both rap2 and the Rig S21N mutation meet the structural limitation, but are known to fail to meet the functional limitation, and it is unknown if Accession Nos. NP_649948, and NP_660252 meet the functional limitation. As a result, one of skill in the art could not conclude that the specification disclosed either a representative number of species of the claimed genus, or a correlation between the claimed structure and the claimed function. Thus one of skill in the art could not conclude that Applicant was in possession of the claimed genus at the time the invention was filed.

Response to Arguments

Applicant's arguments filed 10/22/04 have been fully considered to the extent that they may apply to the rejections set forth above, but they are not persuasive.

With respect to the enablement rejection, Applicant argues that the a mutation at a S21N mutation prevents SEQ ID NO:5 from inhibiting tumor cell growth, thus demonstrating the importance e of this residue. This is evidence that S21N is not a conservative mutation. However, this does not enable the scope of the variants

embraced by claim 40 and dependents, because these claims embrace virtually any nucleic acid encoding a protein that is less than or equal to SEQ ID NO:5 in length, and which inhibits tumor cell growth. The only requirement is that the nucleic acid must encode one or more conservative amino acid substitutions, i.e. amino acids that are different from but functionally similar to one or more amino acids in SEQ ID NO:5. the specification fails to disclose any conservative mutant that retains tumor cell growth inhibition, and as discussed above the state of the art is unpredictable. For these reasons the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 40, 42, 45, and 47 are rejected under 35 U.S.C. 102(b) as being anticipated by Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999).

Lamerdin et al teach a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5, as discussed in the Office Actions of 4/25/03 and 10/20/03. Because the artificial chromosome is double stranded it also comprises the complement to the nucleic acid encoding SEQ ID NO:5. Because bacterial artificial chromosomes are replicated and maintained in bacteria, the disclosure of Lamerdin anticipates claims 45

and 47, requiring a host cell. Limitations regarding the function of the encoded protein, i.e. "inhibits tumor growth" are considered to be inherent in the structure of the protein. Because the sequence of Lamerdin encodes the same protein as SEQ ID NO:5, it is considered to encode a protein that inhibits tumor growth.

Thus Lamerdin anticipates the claims.

Claims 41, 43, 46, 48, 50, and 52 are rejected under 35 U.S.C. 102(b) as being anticipated by Hung et al (Biochem. Biophys. Res. Comm. 269: 718-725, 2000), as evidenced by GenBank Accession No. 1A5E (2/13/98).

Claim 41 is drawn to the genus of isolated or purified nucleic acids "encoding a Rig protein (SEQ ID NO:5) having one or more conservative amino acid substitutions, or a portion thereof, wherein the protein or portion thereof inhibits growth of a tumor cell when contacted with said tumor cell." The specification provides no limiting definition of what is and is not a Rig protein, and defines conservative substitution as substitution with "a different amino acid having similar chemical properties." See e.g. page 21, lines 3-7. As such, the genus of encoded polypeptides must be less than or equal to SEQ ID NO:5 in length, but need have no sequence identity whatsoever with SEQ ID NO:5, as long as it contains at least one amino acid that has a similar chemical properties, and as long as it inhibits tumor cell growth. Therefore, any isolated nucleic acid encoding a tumor suppressor protein less than or equal to SEQ ID NO:5 in length, and containing at least one amino acid having similar chemical properties to a different amino acid in SEQ ID NO:5, will meet the limitations of claim 41.

Hung taught pharmaceutical compositions comprising retroviruses encoding the tumor suppressor $p16^{INK4A}$, as well as pharmaceutical compositions comprising cells containing the $p16^{INK4A}$ retroviruses. Both of these compositions were delivered to rat brains in vivo. See abstract, and page 720, column 2, line 20 to page 723, line 14. Note that position 25 of SEQ ID NO:5 is an L residue, whereas position No; 25 of $p16^{INK4A}$ is a V residue (see attached sequence). This is considered to be a conservative substitution inasmuch as these are both hydrophobic amino acids that differ by only a single methylene group.

The limitation "suitable for administration to a human" can be reasonably interpreted as a physical state that allows injection, such as a suspension of retroviruses. Absent evidence to the contrary, the retroviral composition of Hung could be administered to a human, so it is suitable for administration to a human.

Thus Hung anticipates the claims.

It is noted that the enablement rejection set forth above omits $p16^{INK4A}$ from the enabled scope of the invention. This is considered to be proper because the specificaiton as a whole does not disclose or contemplate the use of $p16^{INK4A}$. The rejected claims are so broad as to embrace subject matter in the prior art that the specification does not reasonably enable.

As currently written, instant claims 35-39 and 44 are indefinite for the reasons set forth above. However, it is noted that Applicant may have intended these claims to be drawn to nucleic acids that encode polypeptides that inhibit tumor cell growth and are at

least 30% identical to SEQ D NO:5. In the interest of compact prosecution, Applicant is advised that such claims would be anticipated by Yu et al (Proc. Nat. Acad. Sci. USA 96: 214-219, 1999) for the following reasons.

Yu taught compositions comprising LIPOFECTAMINE and expression vectors encoding Noey2 sense and antisense, as well as cells comprising these expression vectors. See page 216, first full paragraph. Noey2 is a tumor suppressor that is 46% identical to SEQ ID NO:5. As such Noey2 contains several conservative changes relative to SEQ ID NO:5, see alignment below.

The claim limitations requiring a pharmaceutical composition suitable for administration to a human are considered to be met by the composition of Yu. This is because the specification does not define what is and is not a pharmaceutical composition, nor what is and is not suitable for administration to a human. As a result these limitations were given their broadest reasonble interpretation. A reasonable interpretation of a "pharmaceutical composition" is one that has a detectable effect in vivo, such as expression of a detectable gene. The limitation "suitable for administration to a human" can be reasonably interpreted as a physical state that allows injection, such as a lipofectamine suspension. Absent evidence to the contrary, the lipofectamine composition of Yu could be adminstered to a human, so it is suitable for administration to a human.

BLASTp Alignment for SEQ ID NO:5 (Rig), and Noey2

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Score =  175 bits (444), Expect = 8e-43
Identities = 90/193 (46%), Positives = 124/193 (63%), Gaps = 1/193 (0%)

Rig  : 7   DYRVVVFGAGGVGKSSLVLRFVKGTFRDTYIPTIEDTYRQVISCDKSVCTLQITDTTGSH 66
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            DYRVVV G  GVGKS+L+ ++  G FR  Y+PTIE+TY Q++ C   V +L ITD+
Noey2: 37   DYRVVVVGTAGVGKSTLLHKWASGNFRHEYLPTIENTYCQLLGCSHGVLSLHITDSKSGD 96

Rig  : 67   QFPAMQRLSISKGHAFILVFSVTSKQSLEELGPIYKLIVQIKG-SVEDIPVMLVGNKCDE 125
              A+QR  I++GHAF+LV+SVT K++LEEL   Y+LI +IKG ++   P++LVGNK D+
Noey2: 97   GNRALQRHVIARGHAFVLVYSVTKKETLEELKAFYELICKIKGNNLHKFPIVLVGNKSDD 156

Rig  : 126  TQREVDTREAQAVAQEWKCAFMETSAKMNYNVKELFQELLTLETRRNMSLNIDGKRSGKQ 185
            T REV   +    A EW CAFME SAK + NV+ELF  LL  + +    L    K+S
Noey2: 157  THREVALNDGATCAMEWNCAFMEISAKTDVNVQELFHMLLNYKKKPTTGLQEPEKKSQMP 216

Rig  : 186  KRTDRVKGKCTLM 198
             T+++  KC +M
Noey2: 217  NTTEKLLDKCIIM 229
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Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 30, 31, 40, 42, 49, 51, 64, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999) in view of Yu et al (Proc. Nat. Acad. Sci. USA 96: 214-219, 1999).

Lamerdin taught a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including an open reading frame encoding the amino acid sequence of SEQ ID NO: 5. Lamerdin taught that the sequence encoded a protein similar to RAS-related proteins.

Lamerdin did not teach a pharmaceutical composition comprising a recombinant expression vector encoding SEQ ID NO:5, or the nucleotide sequence of SEQ ID NO:4.

Lamerdin was silent as to the activity of SEQ D NO:5 with regard to effects on tumor cell growth.

Yu taught compositions comprising LIPOFECTAMINE and expression vectors encoding sense and antisense of the Ras-related gene Noey2, as well as cells comprising these expression vectors. See page 216, first full paragraph. Noey2 is a tumor suppressor that is 46% identical to SEQ ID NO:5. As such Noey2 contains several conservative changes relative to SEQ ID NO:5, see alignment below.

It would have been obvious to one of ordinary skill in the art at the time of the invention to prepare expression vectors encoding SEQ ID NO:5 as well as expression vectors for antisense directed against transcriptis encoding SEQ ID NO:5 and to formulate them for transfection of cells as taught by Yu. One would have been motivated to do so because Lamerdin taught that SEQ ID NO:5 was a Ras-related protein, and it is apparent from the teachings of Yu that determining the effects of expression of newly discovered Ras-related genes is essential to understanding their function. Also, Yu teaches that Ras-related genes are involved in tumorigenesis and are therefore of biomedical interest. See abstract, paragraph bridging columns 1 and 2 on page 214.

Limitations regarding the function of the encoded protein, i.e. "inhibits tumor growth" are considered to be inherent in the structure of the protein of Lamerdin. Because the sequence of Lamerdin encodes the same protein as SEQ ID NO:5, it is considered to encode a protein that inhibits tumor growth.

The claim limitations requiring a pharmaceutical composition suitable for administration to a human are considered to be met by the composition of Yu. This is because the specification does not define what is and is not a pharmaceutical composition, nor what is and is not suitable for administration to a human. As a result these limitations were given their broadest reasonble interpretation. A reasonable interpretation of a "pharmaceutical composition" is one that has a detectable effect in vivo, such as expression of a detectable gene. The limitation "suitable for administration to a human" can be reasonably interpreted as a physical state that allows injection, such as a lipofectamine suspension. Absent evidence to the contrary, a lipofectamine composition rendered obvious by Lamerdin and Yu could be adminstered to a human, so it is suitable for administration to a human. Furthermore, absent evidence to the contrary, the transfected cells rendered obvious by Lamerdin and Yu could be adminstered to a human, and so are suitable for administration to a human.

With regard to claims 2 and 31, requiring the nucleic acid sequence of SEQ ID NO:4, the nucleotide sequence of Lamerdin differs from SEQ ID NO:4 by a single, silent base change in a glutamine codon at a position corresponding to position 70 of SEQ ID NO:5. The codon in SEQ ID NO:4 is CAA, whereas the codon reported by Lamerdin et al is CAG. Because CAA and CAG codons both encode glutamine, they are art-recognized equivalents. MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such

substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Hence it would have been prima facie obvious to one of ordinary skill in the art to substitute the sequence of Lamerdin for that of SEQ ID NO:4.

Thus the invention as a whole was prima facie obvious.

Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin (1999) and Yu (1999) as applied to claims 1, 2, 4, 30, 31, 40, 42, 49, 51, 64, and 66 above, and further in view of Hung et al (US Patent 5,922,688, issued 1/10/97).

The teachings of Lamerdin and Yu are summarized above and can be combined to render obvious liposomal pharmaceutical compositions suitable for administration to a human that comprise a recombinant expression vector comprising an open reading frame encoding SEQ ID NO:5.

These references do not teach a replication deficient viral expression vector.

Hung taught that liposomal and viral vehicles, including replication deficient viral vectors, could be used interchangeably for gene delivery. See detailed description paragraphs 63 and 80.

MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). In this case it is clear that

liposomes and replication defective viral vectors were well known in the prior art, and recognized to be interchangeable for the purpose of gene delivery.

Thus the invention as a whole was prima facie obvious.

Claims 1-4, 30, 31, 40, 42, 49, 51, 64, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lamerdin et al (GenBank Accession No. AC006538, published 2/7/1999), in view of Kimmelmann et al (Oncogene (1997) 15(22): 2675-2685), Der et al (US Patent 6,077,686, issued 6/20/2000), and Baker et al (Nucl. Acids. Res. (1997) 25(10): 1950-1956).

In the previous Office Action sent 5/19/04, this rejection was applied to claims 30 and 31. It still applies to these claims, and is now applied to new claims 40, 42, 49, 51, 64, and 66. Due to amendments to claims 1-4, the rejection now applies to these claims as well.

Lamerdin taught a bacterial artificial chromosome comprising 177 kb of human chromosome 19, including a segment encoding the amino acid sequence of SEQ ID NO: 5. See attached sequence and alignment. Lamerdin teaches that the sequence encodes a protein similar to RAS-related proteins. Limitations regarding the function of the encoded protein, i.e. "inhibits tumor growth" are considered to be inherent in the structure of the protein. Because the sequence of Lamerdin encodes the same protein as SEQ ID NO:5, it is considered to encode a protein that inhibits tumor growth.

Lamerdin did not teach a vector comprising a replication defective virus, or a eukaryotic host cell.

Kimmelmann taught the cloning of a RAS-related gene, its transfer to a plasmid expression vector, and analysis of expression of the encoded protein in eukaryotic cells. See abstract, Fig. 2, panel b, Fig. 4 on page 2679 on page 2677, and Fig. 7, panel a on page 2681.

Der et al taught that expression vectors comprising plasmids or replication defective viruses are functional equivalents. See column 11, lines 58-67.

Baker taught that transfection efficiency of bacterial artificial chromosomes to eukaryotic cells is inefficient. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to transfer the RAS-related open reading frame of Lamerdin to a plasmid or replication-defective virus. One would have been motivated to do so in order to facilitate analysis of the gene and its product because members of the Ras subfamily have been shown to be involved in signal transduction and tumorigenesis, and because determining the function of RAS-related genes is an important step in understanding the complexity of intracellular signaling. See e.g. Kimmelmann abstract and page 2676, column 1, last paragraph prior to Results. One of ordinary skill in the art recognizes that transfer of the sequence from a 177 kb artificial chromosome to a different expression vector such as a plasmid or replication deficient virus would facilitate analysis of the gene, because higher transfection efficiency can be achieved with these vectors (see Baker above). MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent

component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). In this case Der teaches that plasmids and replication defective viruses may be used interchangeably as expression vectors, thus these are art-recognized equivalent components in the context of gene expression, and it would have been prima facie obvious to one of ordinary skill in the art to use either type of vector for the expression and analysis of the sequence of Lamerdin. On the other hand one could have improved the transfection efficiency of the baculovirus clone of Lamerdin by adding to it psoralen-inactivated adenovirus as taught by Baker. Because the adenovirus of Baker is inactivated, it is considered to be replication deficient, thereby meeting the limitations of claim 3.

The claim limitations requiring a pharmaceutical composition suitable for administration to a human are considered to be met by the composition of Yu. This is because the specification does not define what is and is not a pharmaceutical composition, nor what is and is not suitable for administration to a human. As a result these limitations were given their broadest reasonble interpretation. A reasonable interpretation of a "pharmaceutical composition" is one that has a detectable effect in vivo, such as expression of a detectable gene. The limitation "suitable for administration to a human" can be reasonably interpreted as a physical state that allows injection, such as a lipofectamine suspension. Absent evidence to the contrary, a lipofectamine composition rendered obvious by Lamerdin and Yu could be adminstered to a human, so it is suitable for administration to a human. Furthermore, absent

evidence to the contrary, the transfected cells rendered obvious by Lamerdin and Yu could be adminstered to a human, and so are suitable for administration to a human.

With regard to claims 2 and 31, requiring the nucleic acid sequence of SEQ ID NO:4, the nucleotide sequence of Lamerdin differs from SEQ ID NO:4 by a single, silent base change in a glutamine codon at a position corresponding to position 70 of SEQ ID NO:5. The codon in SEQ ID NO:4 is CAA, whereas the codon reported by Lamerdin et al is CAG. Because CAA and CAG codons both encode glutamine, they are art-recognized equivalents. MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Hence it would have been prima facie obvious to one of ordinary skill in the art to substitute the sequence of Lamerdin for that of SEQ ID NO:4.

Thus the invention as a whole was *prima facie* obvious.

Response to Arguments

Applicant's arguments filed 10/22/04 have been fully considered to the extent that they may apply to the rejections set forth above, but they are not persuasive.

Applicant's arguments are directed to whether or not the cited art renders obvious a pharmaceutical composition comprising a nucleic acid encoding SEQ ID

NO:5. Applicant indicates correctly that the function of SEQ ID NO:5 was unknown prior to filing of the instant application. So, Applicant argues that there was no appreciation that Rig was a tumor suppressor protein, and one would not have been motivated to make a pharmaceutical composition suitable for administration to a human. This argument is unpersuasive for the reaons set forth above in the rejections, i.e. the specification does not provide any definition of a pharmaceutical definition or what is suitable for administration to a human. As such these limitations have been interpreted broadly. For example, a pharmaceutical composition was interpreted to embrace compositions that would reasonably be expected to have an effect in vivo, such as expression of an encoded gene. Compositions suitable for administration to a human were interpreted to include those that have a physical form allowing administration to a human, such as liposomal or viral compositions. For this reason the rejections are considered proper.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

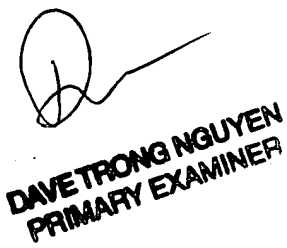
Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, John Leguyader, be reached at 571-272-0760. The official central fax number is 703-872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Richard Schnizer, Ph.D.



Alignments for SEQ ID NO:5 (Rig) with Medline document number 8204955 and NCBI Accession Nos. NP_649948, and NP_660252

Medline document number 8204955

```
>gi|10518344|ref|NP_066361.1|   RAP2A, member of RAS oncogene family [Homo
sapiens]
 gi|47683065|gb|AAH70031.1|   RAP2A, member of RAS oncogene family [Homo
sapiens]
 gi|27371061|gb|AAH41333.1|   RAP2A, member of RAS oncogene family [Homo
sapiens]
 gi|20147721|gb|AAM12628.1|   Ras family small GTP binding protein RAP2A
[Homo sapiens]
 gi|25047734|gb|AAN71845.1|   RbBP-30 [Homo sapiens]
 gi|35861|emb|CAA31052.1|   unnamed protein product [Homo sapiens]
 gi|88914|pir||S03180   transforming protein rap2 - human
 gi|131852|sp|P10114|RP2A_HUMAN   Ras-related protein Rap-2a (RbBP-30)
          Length = 183

 Score =  168 bits (390), Expect = 2e-40
 Identities = 81/161 (50%), Positives = 112/161 (69%), Gaps = 8/161 (4%)

Rig  : 7   DYRVVVFGAGGVGKSSLVLRFVKGTFRDTYIPTIEDTYRQVISCDKSVCTLQITDTTGSH 66
           +Y+VVV G+GGVGKS+L ++FV GTF + Y PTIED YR+ I  D S   L+I DT G+
Sbjct: 3   EYKVVVLGSGGVGKSALTVQFVTGTFIEKYDPTIEDFYRKEIEVDSSPSVLEILDTAGTE 62

Rig  : 67  QFPAMQRLSISKGHAFILVFSVTSKQSLEELGPIYKLIVQIKGSVEDIPVMLVGNKCD-E 125
           QF +M+ L I  G  FILV+S+ ++QS +++ P+   I+++K   E +PV+LVGNK D E
Sbjct: 63  QFASMRDLYIKNGQGFILVYSLVNQQSFQDIKPMRDQIIRVK-RYEKVPVILVGNKVDLE 121

Rig  : 126 TQREVDTREAQAVAQEWKCAFMETSAK---MNYNVKELFQE 163
           ++REV + E +A+A+EW C FMETSAK   M   V ELF E
Sbjct: 122 SEREVSSSEGRALAEEWGCPFMETSAKSKTM---VDELFAE 159
```

NCBI Accession No. NP_6499

```
Shibata et al Genome Res. 10 (11), 1757-1771 (2000)
>gi|21644583|ref|NP_660252.1|   DIRAS family, GTP-binding RAS-like 1 [Mus
musculus]
 gi|34785819|gb|AAH57556.1|   DIRAS family, GTP-binding RAS-like 1 [Mus
musculus]
 gi|16508174|gb|AAL17967.1|   small GTP-binding tumor suppressor 1 [Mus
musculus]
          Length = 198

 Score =  600 bits (1409), Expect = e-170
 Identities = 186/198 (93%), Positives = 193/198 (97%)

Rig  : 1   MPEQSNDYRVVVFGAGGVGKSSLVLRFVKGTFRDTYIPTIEDTYRQVISCDKSVCTLQIT 60
           MPEQSNDYRVVVFGAGGVGKSSLVLRFVKGTFRDTYIPTIEDTYRQVISCDKSVCTLQIT
Sbjct: 1   MPEQSNDYRVVVFGAGGVGKSSLVLRFVKGTFRDTYIPTIEDTYRQVISCDKSVCTLQIT 60
```

```
Rig:   61  DTTGSHQFPAMQRLSISKGHAFILVFSVTSKQSLEELGPIYKLIVQIKGSVEDIPVMLVG 120
           DTTGSHQFPAMQRLSISKGHAFILVFSVTSKQSL+EL PIYKLIVQIKGSVEDIP+MLVG
Sbjct: 61  DTTGSHQFPAMQRLSISKGHAFILVFSVTSKQSLDELSPIYKLIVQIKGSVEDIPIMLVG 120

Rig:   121 NKCDETQREVDTREAQAVAQEWKCAFMETSAKMNYNVKELFQELLTLETRRNMSLNIDGK 180
           NKCDETQREV TREAQAVAQEWKCAFMETSAKMNYNVKELFQELLTLETRR++SL++DGK
Sbjct: 121 NKCDETQREVHTREAQAVAQEWKCAFMETSAKMNYNVKELFQELLTLETRRSVSLSVDGK 180

Rig:   181 RSGKQKRTDRVKGKCTLM 198
           RS KQKR DR+KGKC LM
Sbjct: 181 RSSKQKRADRIKGKCALM 198
```

NCBI Accession No. NP_660252

>gi|24645521|ref|NP_649948.1| CG8500-PA [Drosophila melanogaster]

Drosophila

Length = 233

Score = 392 bits (919), Expect = e-108
Identities = 141/188 (75%), Positives = 159/188 (84%), Gaps = 6/188 (3%)

```
Rig  : 2   PEQSNDYRVVVFGAGGVGKSSLVLRFVKGTFRDTYIPTIEDTYRQVISCDKSVCTLQITD 61
           PEQSNDYRVVVFGAGGVGKSSLVLRF+KGTFR++YIPTIEDTYRQVISC+K++CTLQITD
Sbjct: 13  PEQSNDYRVVVFGAGGVGKSSLVLRFIKGTFRESYIPTIEDTYRQVISCNKNICTLQITD 72

Rig  : 62  TTGSHQFPAMQRLSISKGHAFILVFSVTSKQSLEELGPIYKLIVQIKGS-VEDIPVMLVG 120
           TTGSHQFPAMQRLSISKGHAFILV+SV SKQSLEEL PI+ LI ++KG+ + +IPVMLVG
Sbjct: 73  TTGSHQFPAMQRLSISKGHAFILVYSVCSKQSLEELRPIWALIKELKGADIPNIPVMLVG 132

Rig  : 121 NKCDETQ--REVDTREAQAVAQEWKCAFMETSAKMNYNVKELFQELLTLETRRNMSLNID 178
           NKCDET   REV   E QA A  W  +FMETSAK N+NV ELFQELL +E  R +SL +D
Sbjct: 133 NKCDETAELREVSQAEGQAQATTWSISFMETSAKTNHNVTELFQELLNMEKTRTVSLQLD 192

Rig  : 179 GKRSGKQK 186
            K   KQK
Sbjct: 193 TK---KQK 197
```

DAVE TRONG NGUYEN
PRIMARY EXAMINER

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L1             2 SEA PLU=ON  BACTERIAL ARTIFICIAL CHROMOSOME AND IMMUNI? AND
                 (RABBIT OR MOUSE) AND ANTIBODY
                 D BIB AB 1 2

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     ON 05 JAN 2005
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L3             6 DUP REM L2 (8 DUPLICATES REMOVED)
                 D BIB AB 1-6

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                 D TI 1-10
                 D BIB AB 8

L5             6 NOEY2
   => d bib ab 1-6

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2005 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s rap2 and tumor suppressor
            84 RAP2
        579251 TUMOR
        256127 TUMORS
        697101 TUMOR
                 (TUMOR OR TUMORS)
         54185 SUPPRESSOR
          4064 SUPPRESSORS
         56351 SUPPRESSOR
                 (SUPPRESSOR OR SUPPRESSORS)
         24825 TUMOR SUPPRESSOR
                 (TUMOR(W)SUPPRESSOR)
L1            4 RAP2 AND TUMOR SUPPRESSOR

   => d bib ab 1-4

FILE 'MEDLINE' ENTERED AT 07:00:04 ON 06 JAN 2005

 FILE LAST UPDATED: 5 JAN 2005 (20050105/UP).  FILE COVERS 1950 TO DATE.
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 On December 19, 2004, the 2005 MeSH terms were loaded.

 OLDMEDLINE now back to 1950.

 MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the
 MeSH 2005 vocabulary.  See http://www.nlm.nih.gov/mesh/ and
 http://www.nlm.nih.gov/pubs/techbull/nd03/nd03_mesh.html for a
 description of changes.

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> s p21 and ras and tumor suppressor
         14214 P21
         27080 RAS
             1 RASES
         27081 RAS
                 (RAS OR RASES)
        579444 TUMOR
        256195 TUMORS
        697322 TUMOR
                 (TUMOR OR TUMORS)
         54194 SUPPRESSOR
          4066 SUPPRESSORS
         56361 SUPPRESSOR
                 (SUPPRESSOR OR SUPPRESSORS)
         24830 TUMOR SUPPRESSOR
                 (TUMOR(W)SUPPRESSOR)
L1         256 P21 AND RAS AND TUMOR SUPPRESSOR

=> s l1 and (tumor suppressor (4a) (p21 or ras))
        579444 TUMOR
        256195 TUMORS
        697322 TUMOR
                 (TUMOR OR TUMORS)
         54194 SUPPRESSOR
          4066 SUPPRESSORS
         56361 SUPPRESSOR
                 (SUPPRESSOR OR SUPPRESSORS)
         24830 TUMOR SUPPRESSOR
                 (TUMOR(W)SUPPRESSOR)
         14214 P21
         27080 RAS
             1 RASES
         27081 RAS
                 (RAS OR RASES)
           252 TUMOR SUPPRESSOR (4A) (P21 OR RAS)
L2          38 L1 AND (TUMOR SUPPRESSOR (4A) (P21 OR RAS))
L3         451 P16 (3A) TUMOR SUPPRESSOR
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L4          23 L3 AND INHIBIT? AND VIVO
=> d ti 1-23
=> d bib ab 12
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S15903	U	PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD	20030059771.pn. and pharm$	2005-01-05 09:22:40	
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